REMARKS

As a preliminary matter, on August 8, 2002, the representative for the Applicant filed a third request for a filing receipt. To date, no filing receipt has been received from the Patent Office in the above-referenced application. Please send the undersigned attorney a copy of the filing receipt. In addition, there is a discrepancy with regard to the national phase filing date. On October 18, 2002, the undersigned talked to the Examiner and it was determined that the date was in error. The Examiner stated that the request under 35 U.S.C. § 371 was received on August 30, 2001. Therefore, the national phase filing date should be **August 30, 2001** rather than January 1, 2002, as shown on the cover sheet of the present Office Action. Correction is respectfully requested.

The Applicant hereby submits with this Response a paper copy of the Sequence Listing (attached as Exhibit A) and a copy of the sequence listing in computer readable format (attached in a disk pocket as Exhibit B). The Sequence Listing submitted in computer readable format, along with this Amendment, is identical to the written on paper Sequence Listing added to the application by this Amendment. In addition, the specification has been amended to include the Sequence Listing and to add the sequence identifiers for each listed sequence. Favorable reconsideration of this application is requested in view of the above amendments and following remarks.

I. Rejections under 35 U.S.C. 102

Claims 27-28, 30-33, 35-42, 44, and 48-52 were rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. (U.S. Patent No. 5.942,391). Independent claim 27 is drawn to a method of screening for copy number of target nucleic acid sequences in a sample of genetic material. The method of claim 27 includes introducing to the sample a plurality of different genetic probes suitable to hybridise with respective target sequences and all flanked by the same or substantially the same primer bonding sites, subjecting the sample to conditions favoring hybridization of the probes to their respective sequences, and amplification of sample-bound probes using a pair of primers, wherein analysis of the respective amounts of amplified probes provides for quantitative determination of the copy number of the respective nucleic acid sequences in the sample.

The Office Action states that Zhang discloses a method of screening for copy number of target

nucleic acid sequences in a sample of genetic material comprising the limitations set forth in claims 27-28, 30-33, and 35-38 of the instant application. However, in column 3, beginning at line 30, the Zhang reference discloses that the amplification probes, which in the method may be covalently joined end to end, form a contiguous ligated amplification sequence. It also adds that the assembly of the amplifiable DNA by ligation increases specificity, and makes possible the detection of a single mutation in a target. Thus, Zhang involves a method which employs non-overlapping oligonucleotide probes that ligate to adjacent regions in a target nucleic acid sequence. Thus, the invention of Zhang, requires the probes to be ligated. This requirement is emphasized throughout the Zhang reference as an important feature of the invention.

By contrast, the present invention does not involve ligation and is, therefore, considerably and advantageously simpler than the invention of Zhang. The method of Zhang, as compared to that of the present invention, differs fundamentally in the way in which sequence specificity is achieved. In using ligation, Zhang employs the requirement for the two half probes (or parts of the gapped probe) to be juxtaposed before joining by ligase to solve the specificity problem. Ligase will only do its work when the two probes are brought together by annealing to the right template. In the present invention, the specificity is derived purely from the hybridization and washing steps. Therefore, simple hybridization and recovery of a preformed amplifiable probe is not taught by the Zhang reference. Because the method of the instant claim 27 is not taught by the Zhang reference, withdrawal of the rejection is respectfully requested.

Claims 51 and 52 have been rejected as being anticipated by the Zhang reference. Claim 51 claims a set of probes adapted for use in performing the method according to claim 27 (recited above). Claim 52 claims a kit for performing the method of claim 27 including, among other things, a probe set. Because the present claims 51 and 52 involve probes for use in the method of claim 27, which operates by way of hybridization, not ligation, as discussed above, neither the probes of claim 51 nor the kit of claim 52 are anticipated by the Zhang reference. Accordingly, withdrawal of the rejection is respectfully requested.

In view of the foregoing, independent claim 27 is not anticipated by Zhang. In addition, claims 28-52 depend from claim 27. These dependent claims are patentably distinguished from the cited reference for the same reasons as the claim 27. As such, withdrawal of the rejection of these claims is, likewise, respectfully requested.

II. Rejections under 35 U.S.C. 103

Claim 34 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang and further in view of Concannon (U.S. Patent No. 5,770,372). Claim 34 claims the use of the method of claim 27 for screening sequences of different exons in a eukaryotic gene. As shown above, the method of claim 27 is not taught by the Zhang reference. Concannon does not cure the deficiencies of Zhang because it, likewise, fails to teach modifying Zhang to eliminate the use of ligation in the amplification sequence. Therefore, claim 34 is not obvious in view of the combination of Zhang and Concannon and withdrawal of the rejection is respectfully requested.

Claim 47 is directed to a method of claim 27 where the unbound probes and primer are thoroughly washed away from bound probes following hybridization prior to analysis. Zhang does not teach washing away the unbound probes and primers following hybridization and prior to analysis but rather Zhang discloses washing away unbound reactants and other materials in the sample, followed by detection of the ligated amplification sequence. The method of Zhang operates through a two-step process where the target nucleic acid is hybridized to the probe followed by ligation of the probe into a circular molecule (see column 18, lines 25-66). On the other hand, the present invention is directed to hybridization followed by washing to detect the amplification sequence. Yamane also does not cure the deficiencies of Zhang because it does not teach modifying Zhang to eliminate the use of ligation in the amplification sequence. Therefore, claim 47 is patentable over the cited references and withdrawal of the rejection is respectfully requested.

In view of the foregoing amendment and remarks, claims 27-52 are now in condition for allowance. A favorable response to this Amendment in the form of a Notice of Allowance is hereby solicited.

Dated: 11/11/02

Respectfully submitted,

Michael A. Miller
Reg. No. 50,732

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The Sequence Listing was added to page 12 of the specification.
The following paragraph in the specification have been amended:

The third full paragraph beginning on page 6 and extending to the top of page 7.

The initial mix of 43 probes was subcloned from plasmids and plasmid fragments known from sequencing or hybridisation not to contain dispersed repeat elements; in the case of one of the Y-linked probes (SRY), a 1360bp fragment was amplified using primers SRYA, SEQ ID NO: 3, (5′GCAGTAGAGCAGTCAGGGAG3′) and SRYB, SEQ ID NO: 4, (5′GGGGAGAGAAAGAAACAAGTTTG3′). Other sources of cloned genomic DNA were: chromsome 1, pJBT2 (JALA, unpublished); chromosome 17, pYNZ22 (Nakamura et al., 1988); chromosome 18, pMS440 (Armour et al., 1990); chromosome 22, pMS632c (Armour et al., 1995); chromosome X, pMS613 (Armour et al., 1990). After isolation of the genomic insert and digestion with frequently-cutting restriction enzymes producing blunt ends (generally double digestion with *Alu*I plus *Hae*III), the resulting smaller fragments were cloned into the *Eco*RV site of pZero2 (InVitrogen) and propagated in *E.coli* TOP10 (InVitrogen). Care was taken to avoid repeat regions in DNA from minisatallite containing clones.

The first full paragraph on page 7

With reference to Fig. 6, probes prepared by cloning blunt-ended restriction fragments from primary clones into the *Eco*RV site of pZero2 (InVitrogen) were amplified directly from bacterial cells (Sandhu et al., 1989) using flanking vector primers PZA, SEQ ID NO: 1, (5′AGTAACGGCCGCCAGTGTGCTG3′) and PZB, SEQ ID NO: 2, (5′CGAGCGGCCGCCAGTGTGATG3′). The positions of these primers in the pZero-2 cloning site is shown in figure 6. PCR was carried out in Advanced Biotechnologies Buffer IV (75mM Tris-HCl pH8.8, 20mM $(NH_4)_2SO_4$, 0.01% Tween), with 0.2mM each dNTP, 1mM $MgCl_2$, 0.2μM each primer and 0.05U/μl Taq DNA polymerase (Advanced Biotechnologies). Reactions (generally 10μl) were subjected to 25 cycles of (95°C for 1 minute/70°C for 1 minute). Products amplified using ^{33}P end- [labeled] labeled PZA were separated on denaturing 6% polyacrylamide/50% urea gels and probe mixes assembled such that the mobilities of all probes were distinct.